PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
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Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 17 March 1998 (17.03.98)	
International application No. PCT/EP97/04774	**Applicant's or agent's file reference** HF 96177/PCT/061
International filing date (day/month/year) 02 September 1997 (02.09.97)	**Priority date** (day/month/year) 04 September 1996 (04.09.96)
Applicant DEL SOLDATO, Piero et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   26 February 1998 (26.02.98)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 213/00, 213/74, 231/1285, 239/91, 285/28, 295/14, 307/52, 311/00, 311/22, 333/22, 409/12, 417/12, A61K 31/405, 31/245, 31/63

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MI96A001821 4 September 1996 (04.09.96) IT

(71) Applicant *(for all designated States except US)*: NICOX S.A. [FR/FR]; 45, avenue Kléber, F-75116 Paris (FR).

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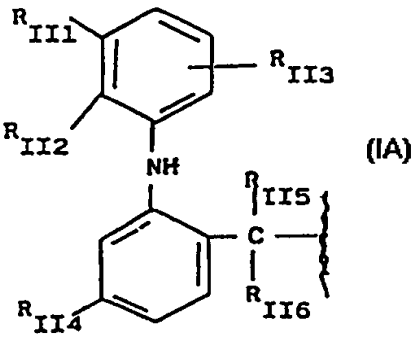
Without international search report and to be republished upon receipt of that report.

(54) Title: NITRIC ESTER DERIVATIVES AND THEIR USE IN URINARY INCONTINENCE AND OTHER DISEASES

(57) Abstract

Use of the following groups of compounds or their compositions for the preparation of medicaments for the treatment of urinary incontinence, such compounds having general formula: $A\text{-}X_1\text{-}NO_2$ or their salts, where $A = R(COX)_t$ and where t is an integer 0 or 1; X = O, NH, NR_{1C}, where R_{1C} is a linear or branched alkyl having from 1 to 10 C atoms; R is (IA) where t = 1 and X_1 is equal to -YO- where Y is a C_1-C_{20} alkylene, C_5-C_7 cycloalkyl or oxyalkyl derivatives.



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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
HF 9617/PCT/061		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 97/04774	02/09/1997	04/09/1996
Applicant		
NICOX S.A. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 9 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (see Box I).

2. [X] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [ ] the text is approved as submitted by the applicant.
   - [X] the text has been established by this Authority to read as follows:

   Nitric ester derivatives and their use in urinary incontinence and other diseases

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 97/04774

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claims Nos.: 1(partially)-6(partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

In view of the great number of compounds for which protection is being sought in claim 1, the search has been restricted for economical reasons to compounds of the examples and the first inventive concept.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

1. Claims: 1,2

Use of the compounds A-X1-NO2, A being R(COX)t and R being choosen from groups I A) to V A) for the preparation of medicaments for treating urinary incontinence

The subject matter of the present application is not unitary contrary to the requirements of R.13. 1 PCT.

With respect to the present claims 1 to 6, the ISA is unable to see any common inventive concept linking these claims as:

The subject matter of claim 1 is directed to the USE of compounds of a general formula A-X1-NO2, with A being R(COX)- and R is choosen from groups I a) to V A) for the manufacture of a medicament for treating URINARY INCONTINENCE.

Claims 3 and 4 are directed to a sub-class of said compounds (or compositions containing them) of the general formula above, R is choosen from group V A)

The subject matter of claim 5 is directed to a sub-class of compounds of a general formula A-X1-NO2, with A being R(COX)- and R is choosen from groups V A)(or compositions containing said compounds) for use as medicament for treating:
a) musculoskeletal disease of an inflammatory nature
b) respiratory diseases
c) gynaecological or obstetrical diseases
d) vascular diseases
e) gastrointestinal tumors

The subject matter of claim 6 is directed to the use of compounds of a general formula A-X1-NO2, with A being R(COX)- and R is choosen from groups I a) to VI A) for the manufacture of a medicament for treating diseases b) to e) listed above

With respect to the various definitions of R given in the present application, it appears that they shall necessarily comprise a -O-NO2 moiety as SOLE structural requirement. Organic nitrates comprising the same moiety -O-NO2 are well known in therapy of cardiovascular diseases (see WO9201688 or WO9421618). The compounds when R belongs to the groups I A) to IV A) and VI A) are already known for therapy (see WO9530641).

=> In other words, the present application covers the use of compounds comprising said -O-NO2 moiety for various therapeutic uses.

As some of the compounds are already known in therapy, the ISA comes to the conclusion that the present application is directed to the subsequent therapeutical uses of partially known compounds. The ISA is unable to identify any common inventive concept which links the subsequent claimed

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

diseases: urinary incontinence and the diseases a)-e) listed above. Accordingly, the present application is not unitary.

For instance, claim 6 when it refers to the compounds when R belongs to the groups I A) to IV A) and VI A) comprises the following 4 different inventions:

1) use of compounds of formula A-X1-NO2 with A= R(COX)t, R is a moiety according to any of groups I a)- IV A) for the preparation of medicaments for treating respiratory diseases
2) use of compounds of formula A-X1-NO2 with A= R(COX)t, R is a moiety according to any of groups I a)- IV A) for the preparation of medicaments for treating gynaecological or obstetrical diseases
3) use of compounds of formula A-X1-NO2 with A= R(COX)t, R is a moiety according to any of groups I a)- IV A) for the preparation of medicaments for treating vascular diseases
4) use of compounds of formula A-X1-NO2 with A= R(COX)t, R is a moiety according to any of groups I a)- IV A) for the preparation of medicaments for treating gastrointestinal tumors

A comprehensive search for the subsequent inventions would have caused major additional searching efforts

Accordingly, the present application comprises the following 6 inventions:

1st invention:
see above Subject 1

2nd invention
claims 3-5 and 6(partially)
use of compounds of formula A-X1-NO2 with A= R(COX)t, R is a moiety according to any of groups V A) for the preparation of medicaments for treating respiratory diseases, gynaecological or obstetrical diseases, vascular diseases or gastrointestinal tumors

3rd invention:
claim 6(part.)
use of compounds of formula A-X1-NO2 with A= R(COX)t, R is a moiety according to any of groups I a)- IV A) and VI A) for the preparation of medicaments for treating respiratory diseases

4th invention:
claim 6 (part.)
use of compounds of formula A-X1-NO2 with A= R(COX)t, R is a moiety according to any of groups I a)- IV A) and VI A) for the preparation of medicaments for treating gynaecological or obstetrical diseases

5th invention:
claim 6(part.):
use of compounds of formula A-X1-NO2 with A= R(COX)t, R is a moiety according to any of groups I a)- IV A) and VI A) for the preparation of medicaments for treating vascular diseases

6th invention:

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

claim 6 (part.)
use of compounds of formula A-X1-NO2 with A= R(COX)t, R is a moiety according to any of groups I a)- IV A) and VI A) for the preparation of medicaments for treating gastrointestinal tumors

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/04774

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C203/04 C07C211/46 C07C311/00 C07D209/08 C07D209/48
C07D209/72 C07D213/00 C07D213/74 C07D231/12 C07D239/91
C07D285/28 C07D295/14 C07D307/52 C07D311/00 C07D311/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ROUSSEAU P ET AL: "URINARY INCONTINENCE IN THE AGED PART 2: MANAGEMENT STRATEGIES" GERIATRICS, vol. 47, no. 6, January 1992, pages 37-40,47, XP002050834 * p.47, 2nd col., Functional incontinence, 1st par. * ---	1,2
X	WO 95 30641 A (NICOX LTD; DEL SOLDATO PIERO (IT); SANNICOLO FRANCESCO (IT)) 16 November 1995 cited in the application * p.5, last par.-p.6, l.12; p.53, last par-p.58, bottom; claims 1-7 * ---	1-6
	-/--	

[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
24 March 1998	09. 04. 98

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/04774

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D333/22 C07D409/12 C07D417/12 A61K31/215 A61K31/245
A61K31/405 A61K31/63

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 04484 A (CORLAY SL ;METGROVE LTD (IE); MATJI JOSE ANTONIO (ES); ALCAIDE ANT) 3 March 1994 * p.2, l.12-20; claims 1-7 *	5,6
Y	see claims 1-7 ---	1-4
A	WO 94 21618 A (CERMOL SA ;SUNKEL CARLOS (ES); FAU MIGUEL (ES); PRIEGO JAIME G (ES) 29 September 1994 see claims 1-10 ---	1,2
A	WO 92 01668 A (ITALFARMACO SPA) 6 February 1992 see the whole document ---	1,2
P,Y	WO 97 25984 A (SCHERING AG ;UNIV TEXAS (US)) 24 July 1997 * p.4, l.21-29; claims 1 and 8 * --- -/--	1,2

[X] Further documents are listed in the continuation of box C.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 439 938 A (SNYDER SOLOMON H ET AL) 8 August 1995 see claims 1,24	1,2,5,6
X	US 5 480 999 A (CHABRIER DE LASSAUNIERE PIERRE ET AL) 2 January 1996 * col.1, l.11-col.2, l.43; claims 1-14 *	3-6
X	WO 94 13635 A (MERCK FROSST CANADA INC ;FORD HUTCHINSON ANTHONY W (CA); KENNEDY B) 23 June 1994 cited in the application * p.13, l.20-p.14, l.6; p.26, compound 12 *	3-6
P,X	WO 97 16405 A (NICOX S A ;DEL SOLDATO PIERO (IT); SANNICOLO FRANCESCO (IT)) 9 May 1997 see claims 1-6	6
Y	WO 95 13802 A (SCHERING AG ;GARFIELD ROBERT E (US); YALLAMPALLI CHANDRA (US)) 26 May 1995 * p.5, l.16; claims 1-3 *	3-6
Y	WO 96 16645 A (WELLCOME FOUND ;KING S COLLEGE LONDON (GB); BELDER ADAM JULIAN DE) 6 June 1996 * p.1, 1st and 2nd par.; p.3, l.10-13; claims 1-4 *	3-6
Y	WO 96 17604 A (WELLCOME FOUND ;KING S COLLEGE LONDON (GB); BELDER ADAM JULIAN DE) 13 June 1996 * p.1, 1st par.; p.3, l.10-11; claims 1-20 *	3-6
Y	K.F. CHUNG : "Furosemide and other diuretics in asthma" J. ASTHMA, vol. 31, no. 2, 1994, pages 85-92, XP002059907 * Table 1; p.90, conclusion *	3-6
Y	CIRINO ET AL: "Inhibition of inducible NO synthetase expression by novel NSAID derivatives with gastrointestinal sparing properties" BRITISH J. PHARMACOLOGY, vol. 117, 29 March 1996, pages 421-26, XP002059908 see abstract	1-6

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	ANDERSSON K -E ET AL: "NITRIC OXIDE SYNTHASE AND THE LOWER URINARY TRACT: POSSIBLE IMPLICATIONS FOR PHYSIOLOGY AND PATHOPHYSIOLOGY" SCANDINAVIAN JOURNAL OF UROLOGY AND NEPHROLOGY, no. SUPPL. 175, 1995, pages 43-53, XP000670055 see abstract	1-4
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 97/04774

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TERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 97/04774

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

SAMA. Daniele
Sama Patents
Via G.B. Morgani 2
I-20129 Milano
ITALIE

SAMA PATENTS
31 DIC 1998
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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 28.12.98
Applicant's or agent's file reference HF 96177/PCT/061	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP97/04774	02/09/1997	04/09/1996

Applicant
NICOX S.A. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0. Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Senkel, H Tel. (+49-89) 2399-8071

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (PCT/IPEA/416)
HF 9617/PCT/061		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP97/04774	02/09/1997	04/09/1996
International Patent Classification (IPC) or national classification and IPC		
C07D213/00		
Applicant		
NICOX S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 24 sheets.

3. This report contains indications relating to the following items:

I	☒	Basis of the report
II	☐	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☒	Lack of unity of invention
V	☒	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability: citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☒	Certain defects in the international application
VIII	☐	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26/02/1998	18. 12. 98
Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0. Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Uiber, P Telephone No. (+49-89) 2399-8474

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP97/04774

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-63 as originally filed

Claims, No.:

1,2 as received on 10/06/1998 with letter of 08/06/1998

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☒ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose. according to Rule 68.1. not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1. 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1 and 2.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,2
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1,2
Industrial applicability (IA)	Yes:	Claims	1,2
	No:	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

1). a) For the assessment of the present claims 1 and 2 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

b) In Contracting States where such claims are regarded as susceptible of industrial applicability, the following applies

2). The following documents (D1-D18) are referred to in this report; the numbering results from the order of citations found in the Search Report (SR) and it will be adhered to in the rest of the procedure.

3). The present application is not unitary in the sense of R.13.1 PCT. The reasons for this objection can be found in form PCT206 attached to the SR.

4). With respect to the available cited prior art, D1-D18, , it appears that the use of the compounds with general formula A-X1-NO2, according to claims 1 and 2 is novel (Art. 33(2) PCT) as none of these documents reports the use of said derivatives for the treatment of urinary incontinence.

5). a) According to D7, nitric oxide synthetase (NOS) inhibitors are effective for inhibiting micturition (see claim 24).
The present derivatives, nitroxybutylesters of ibuprofen, flurbiprofen, aspirin, ... (see also D15, abstract, item 2) are reported to be effective NOS inhibitors (see p.60-61; D15, abstract, item 6).
Likewise, NSAIDs or COX-2 inhibitors are already known to be effective in the treatment of incontinence (see D1), it can be derived that the present compounds being a combination of a COX-2 inhibitor or a NSAID with a nitroxyester function will be effective in the treatment of urinary incontinence as well.
To the contrary, the Applicant states that said derivatives achieve said therapeutic effect by the combination of their COX-inhibiting effect and their NO release (p.40, 2nd full par.).

b) This contradiction between D7 and the present results is not clarified in the present application.

c) Moreover, a synergism is claimed to occur upon combination of the two therapeutic agents, however, there is no evidence of said effect as the tests diclosed in the application do not report the effect induced by NO release alone.

d) Finally, the tests in the present application have been only carried out with one class of compounds, the NSAIDs or COX-2 inhibitors whereas diuretics of the class V Ad) and V Ae) are claimed as well.
There is no evidence that such combinations may have the same therapeutic activity with a synergistic effect.
It is reminded that any compound or (in the present case) each group of compounds (being claimed) must solve the problem posed, i.e. the treatment of urinary incontinence.
As already acknowledged by the Applicant, diuretics for edema therapy is well known (edema may be one aspect of urinary incontinence), so that the administration of a NO donor together with a diuretic appears to be an obvious combination as D17 already report the positive effect of NO on micturition.
The absence of tachyphylaxis in the case of diuretics is not evidenced (see the description, p.59, l.3-6).

e) In view of the previous items 5 b)-d), the IPEA comes to the conclusion that claims 1 and 2 do not involve an inventive step (Art.33(3) and R.65 PCT).

6) Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1, D6-D8 and D10-D18 are not mentioned in the description, nor are these documents identified therein.

CLAIMS

1. Use of the following groups of compounds, or their compositions, for the preparation of medicaments for the treatment of urinary incontinence, having the general formula:

$$A\text{-}X_1\text{-}NO_2$$

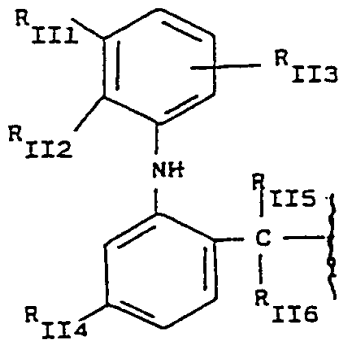
or their salts, where:

A = $R(COX)_t$ where t is an integer 0 or 1;

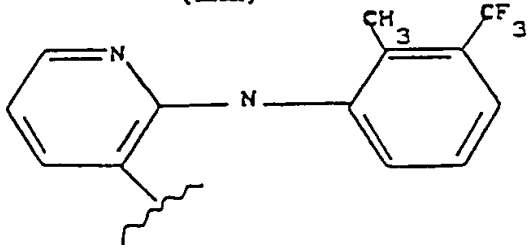
X = O, NH, NR_{1C} where R_{1C} is a linear or branched alkyl having from 1 to 10 C atoms;

R is chosen from the following groups:

* Group I A), where t = 1,



(IAa)



(IAb)

where:

R_{II5} is H, a linear or whenever possible branched C_1-C_3 alkyl;

R_{II6} has the same meanings as R_{II5}, or when R_{II5} is H it can be benzyl;

R_{II1}, R_{II2} and R_{II3} are equal or different one from the other and are hydrogen, linear or whenever possible branched C_1-C_6 alkyl or C_1-C_6 alkoxy, or Cl, F, Br;

R_{II4} is R_{II1} or bromine;

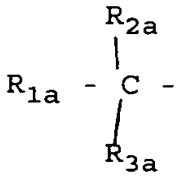
preferred are the compounds where R_{II1}, R_{II2} and R_{II4} are H, and R_{II3} is Cl and R_{II3} is in the ortho position to NH; R_{II5} and R_{II6} are H, X is equal to O, and X_1 is $(CH_2-CH_2-O)_2$;

(I Ab) is the residue of 2-[[2-methyl-3-(trifluoromethyl)phenyl]amino]-3-pyridinecarboxylic acid and when -COOH is present it is known as flunixin.

The compounds preferred are those where X = O;

* II A) chosen from the following:

where, when t = 1, R is

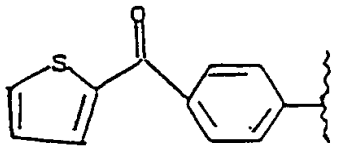


where R_{2a} and R_{3a} are H, a linear or whenever possible

branched substituted or non-substituted C_1-C_{12} alkyl, allyl, with the proviso that when one of the two is allyl the other is H; preferably R_{2a} is H, alkyl has from 1 to 4 C atoms, R_{3a} is H;

R_{1a} is chosen from

II Aa)



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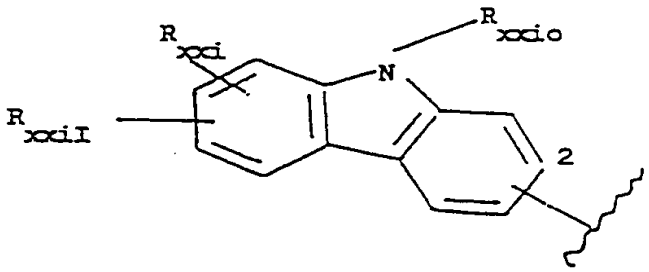
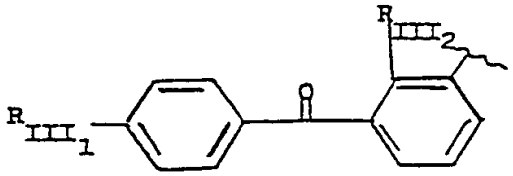


(XXI)



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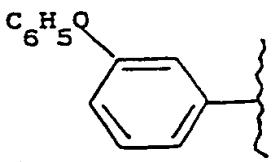

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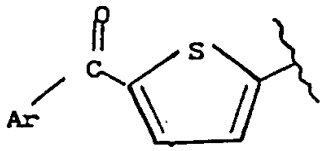

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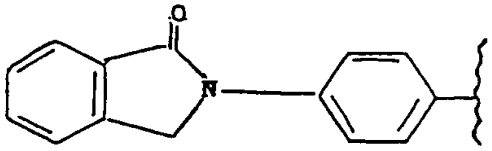

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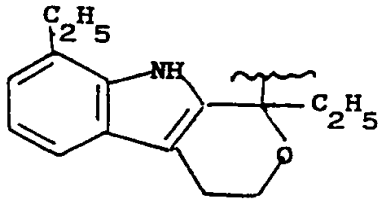

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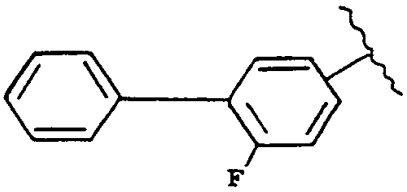

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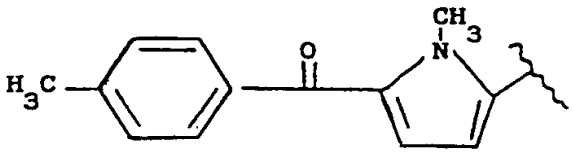

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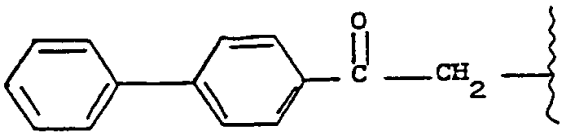


(III)

where meanings are as follows:

- in the compounds of formula (IV), residue of ketoprofen:

R_{III1} is H, SR_{III3} where R_{III3} contains from 1 to 4 C linear or whenever possible branched C atoms;

R_{III2} is H, hydroxy;

preferred are the compounds where R_{III1} and R_{III2} are H, R_{3a} is H, and R_{2a} is methyl, X = O;

- in the compounds of formula (XXI), residue of carprofen:

R_{xxio} is H, a linear or whenever possible branched alkyl having from 1 to 6 carbon atoms, a C_1-C_6 alkoxycarbonyl bound to a C_1-C_6 alkyl, a C_1-C_6 carboxyalkyl, a C_1-C_6 alkanoyl, optionally substituted with halogen, benzyl or halobenzyl, benzoyl or halobenzoyl;

R_{xxi} is H, halogen, hydroxy, CN, a C_1-C_6 alkyl optionally containing OH groups, a C_1-C_6 alkoxy, acetyl, benzyloxy, SR_{xxi2} where R_{xxi2} is a C_1-C_6 alkyl; a perfluoroalkyl having from 1-3 C atoms, a C_1-C_6 carboxyalkyl optio-

nally containing OH groups, NO_2, sulphamoyl, dialkyl sulphamoyl with the alkyl having from 1 to 6 C atoms, or difluoroalkylsulphonyl with the alkyl having from 1 to 3 C atoms;

R_{xxi1} is halogen, CN, a C_1-C_6 alkyl containing one or more OH groups, a C_1-C_6 alkoxy, acetyl, acetamido, benzyloxy,

SR_{III3} is as above defined, a perfluoroalkyl having from 1 to 3 C atoms, hydroxy, a carboxyalkyl having from 1 to 6 C atoms, NO_2, amino, a mono- or dialkylamino having from 1 to 6 C atoms, sulphamoyl, a dialkyl sulphamoyl having from 1 to 6 C atoms, or difluoroalkylsulphamoyl as above defined; or R_{xxi} jointly with R_{xxi1} is an alkylene dioxy having from 1 to 6 C atoms;

preferred are the compounds where R_{xxio} is H, the connecting bridge is at position 2, R_{xxi} is H, R_{xxi1} is chlorine and is in the para position to nitrogen;

R_{3a} is H, R_{2a} is methyl and X is O;

- in the compounds of formula (XXXV), residue of thiaprofenic acid: Ar is phenyl, hydroxyphenyl optionally mono- or polysubstituted with halogen, an alkanoyl or alkoxy having from 1 to 6 C atoms, a trialalkyl having from 1-6 C atoms, preferably from 1-3 C atoms, cyclo-

pentyl o-hexyl o-heptyl, heteroaryl, preferably thienyl, furyl optionally containing OH, pyridyl;

the preferred compounds of formula (XXXV) are those where Ar is phenyl, R_{3a} is H, R_{2a} is methyl and X is O;

- in the compounds of formula (II), residue of suprofen,

the preferred, where R_{3a} = H, R_{2a} = CH_3 and X = O;

- in the compounds of formula (VI),

of which the preferred, indoprofen, when R_{2a} is CH_3 or indobufen, when R_{2a} is equal to H and R_{3a} = CH_3 and X = O;

- in the compounds of formula (VIII),

of which the preferred, etodolac, when R_{3a} = R_{2a} = H and X = O;

- in the compounds of formula (VII),

of which the preferred, fenoprofen, when R_{3a} = H, R_{2a} = CH_3 and X = O;

- in the compounds of formula (III),

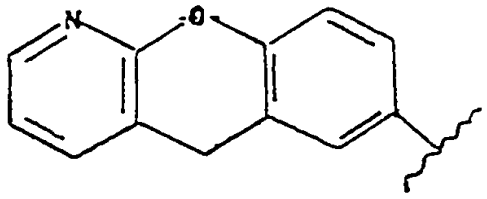
of which the preferred, fenbufen, when R_{3a} = R_{2a} = H and X = O;

- in the compounds of formula (X), residue of tolmetin, when R_{3a} = R_{2a} = H and X = O;

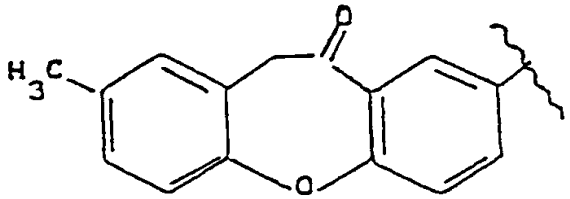
- in the compounds of formula (IX), residue of flurbi-

profen, when R_{3a} = H, R_{2a} = CH_3 and X = O;

II Ab):



IIIa)



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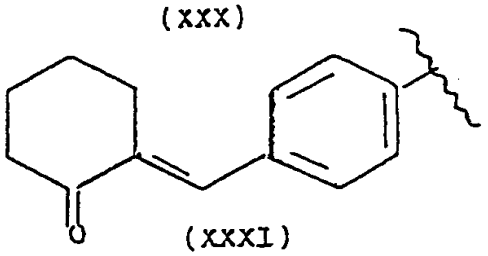

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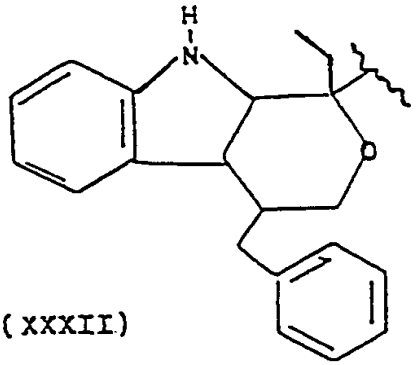

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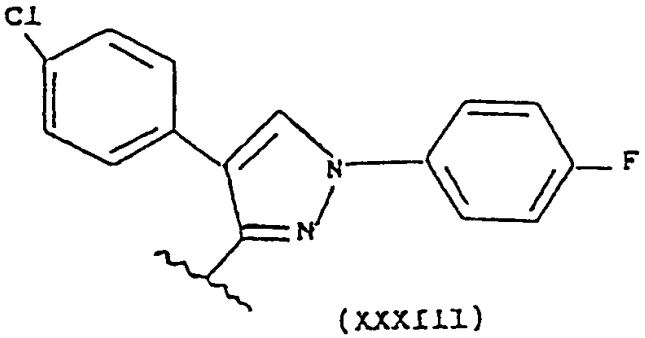

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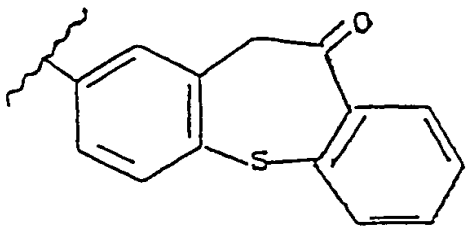

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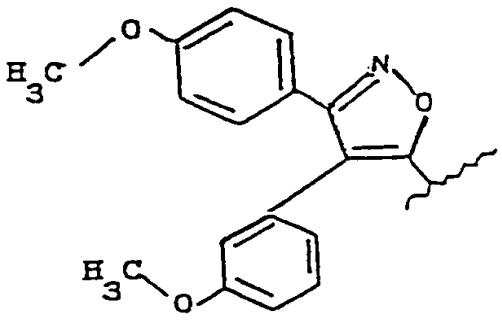


(XXXVII)

where the meanings are as follows:

- when IIIa) contains $-CH(CH_3)-COOH$ it is known as pranoprofen: α-methyl-5H-[1] benzopyran [2,3-b]pyridine-7-acetic acid; preferred R_{2a} = H, R_{3a} = CH_3 and X = O;
- when residue (XXX) contains $-CH(CH_3)-COOH$ it is known as bermoprofen: dibenz [b,f] oxepin-2-acetic acid, preferred is X = O, R_{2a} = H, R_{3a} = CH_3;

- residue (XXXI) is known as CS-670: 2-[4-(2-oxo-1-cyclohexylidenemethyl)phenyl]propionic acid, when the radical is $-CH(CH_3)-COOH$; preferred R_{2a} = H, R_{3a} = CH_3 and X = O;

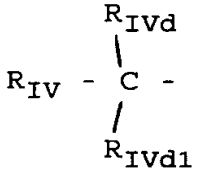
- residue (XXXII) derives from the known pemedolac which contains group $-CH_2COOH$, preferred R_{2a} = R_{3a} = H and X = O;

- when residue (XXXIII) is saturated with $-CH_2COOH$ it is known as pyrazolac: 4-(4-chlorophenyl)-1-(4-fluorophenyl)3-pyrazolyl acid derivatives; preferred R_{2a} = R_{3a} = H and X = O;

- when residue (XXXVI) is saturated with $-CH(CH_3)-COO-$ it is known as zaltoprofen. When the residue is saturated with a hydroxy or amine group or the acid salts, the compounds are known as dibenzothiepin derivatives. Preferred R_{2a} = H, R_{3a} = CH_3 and X = O;

- when residue (XXXVII) is CH_2-COOH it derives from the known mofezolac: 3,4-di(p-methoxyphenyl)isoxazol-5-acetic acid; preferred are R_{2a} = R_{3a} = H, t = 1, X = O.

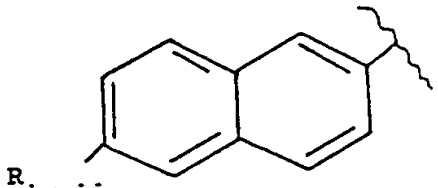
* Group IIIA), where t = 1,



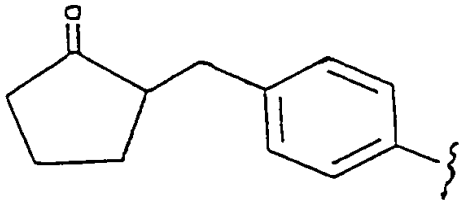
where:

R_{IVd} and R_{IVd1} are at least one H and the other a linear or whenever possible branched C_1-C_6 alkyl, preferably C_1 and C_2, or difluoroalkyl with the alkyl having from 1 to 6 C atoms, preferred is C_1, or R_{IVd} and R_{IVd1} jointly form a methylene group;

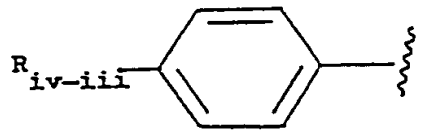
R_{IV} has the following meaning:



(II)



(X)



(III)

where the compounds of group IIIA) have the following meanings:

- in the compounds of formula (II):

R_{IV-II} is an alkyl having from 1 to 6 C atoms, a cycloalkyl having from 3 to 7 C atoms, an alcoxymethyl having from 1 to 7 C atoms, a trifluoroalkyl having from 1 to 3 C atoms, vinyl, ethynyl, halogen, an alkoxy having from 1 to 6 C atoms, a difluoroalkoxy with the alkyl having from 1 to 7 C atoms, an alkoxymethyloxy having from 1 to 7 C atoms, an alkylthiomethyloxy with the alkyl having from 1 to 7 C atoms, an alkylmethylthio with the alkyl having from 1 to 7 C atoms, cyano, difluoromethylthio, a substituted phenyl- or phenylalkyl with the alkyl having from 1 to 8 C atoms; preferably R_{IV-II} is CH_3O, R_{IVd} is H and R_{IVd1} is CH_3, and is known as the residue of naproxen;

X = NH and X_1 is equal to $(CH_2)_4$ or $(CH_2CH_2O)_2$; also preferred is the same compound where X is equal to O;

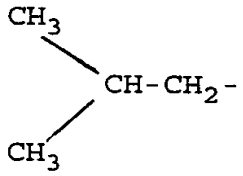
- in the preferred compounds of formula (X), for which the residue of loxoprofen has been shown, R_{IVd} is H and R_{IVd1} is CH_3, X = NH or O and X_1 is equal to $(CH_2)_4$ or $(CH_2CH_2O)_2$;

- in the compounds of formula (III):

R_{IV-III} is a C_2-C_5 alkyl, even branched when possible, a C_2 and C_3 alkyloxy, allyloxy, phenoxy, phenylthio, a cycloalkyl having from 5 to 7 C atoms, optionally sub-

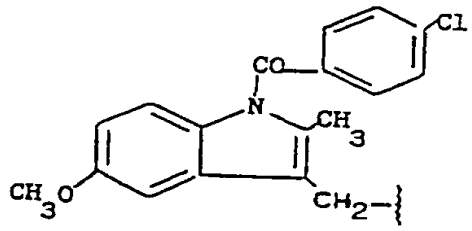
stituted at position 1 by a C_1-C_2 alkyl;

preferred is the compound where R_{IV-III} is



and R_{IVd} = H, R_{IVd1} is CH_3, a compound known as the residue of ibuprofen; X = NH and X_1 is equal to $(CH_2)_4$ or $(CH_2CH_2O)_2$; also preferred is the same compound where X = O;

* Group IV A)



(IV)

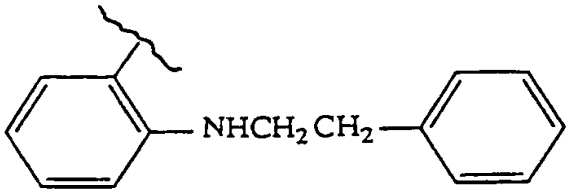
where A = RCOO, t = 1,

of which the residue of the known indomethacin has been shown.

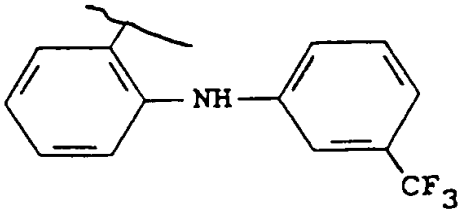
* Group V A) chosen from the following:

- V Aa) fenamates chosen from the following,

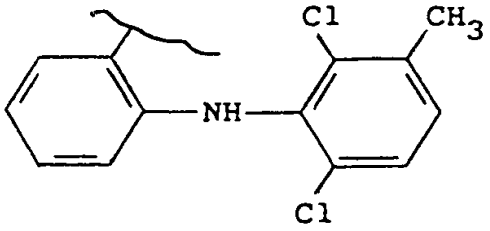
where t = 1



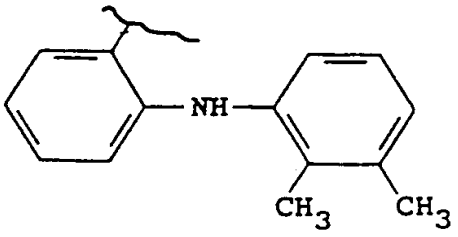
(V Aa1)



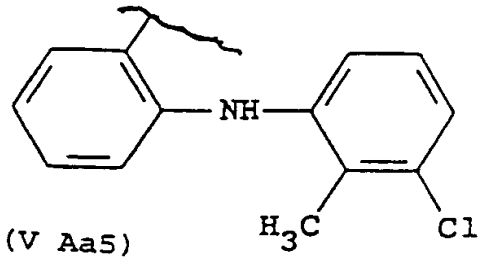
(V Aa2)



(V Aa3)

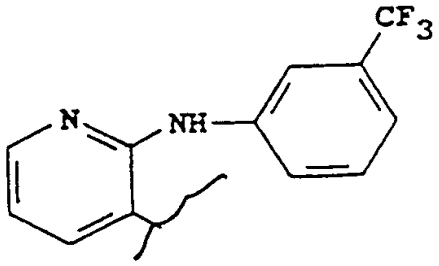


(V Aa4)



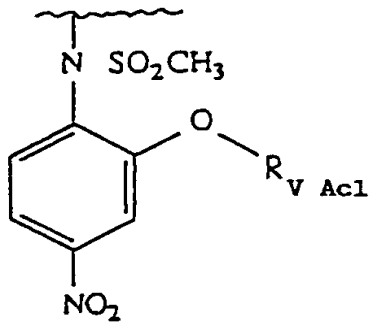
(V Aa5)

- V Ab), derivatives of niflumic acid, where t = 1:

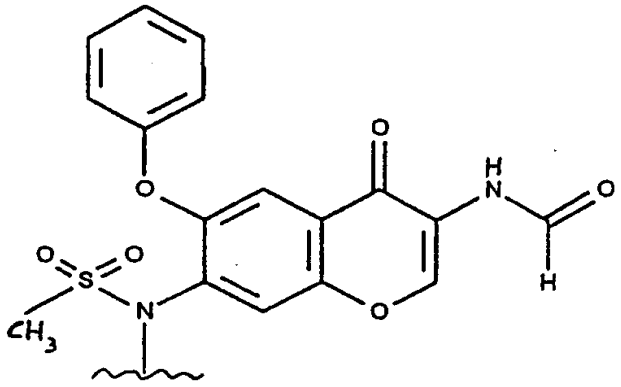


(V Ab1)

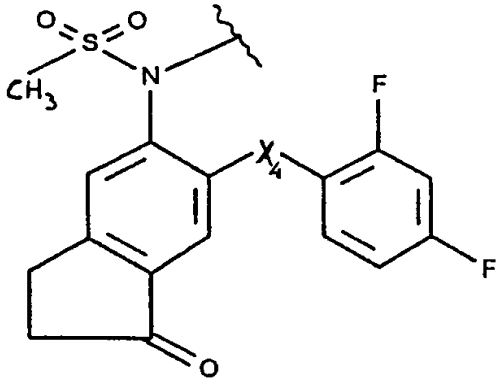
- V Ac), COX_2 inhibitors, where t = 0 and R is as follows:



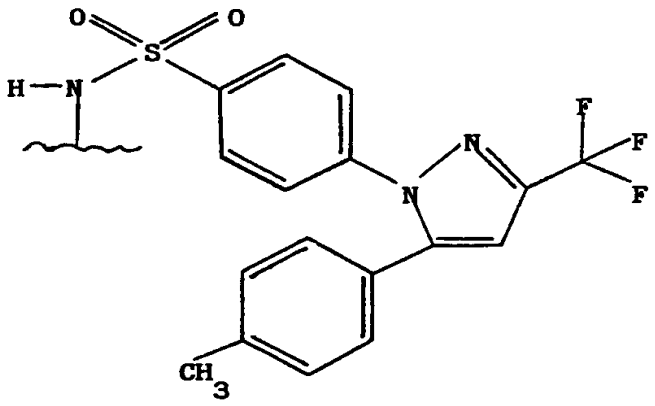
(V Ac1)



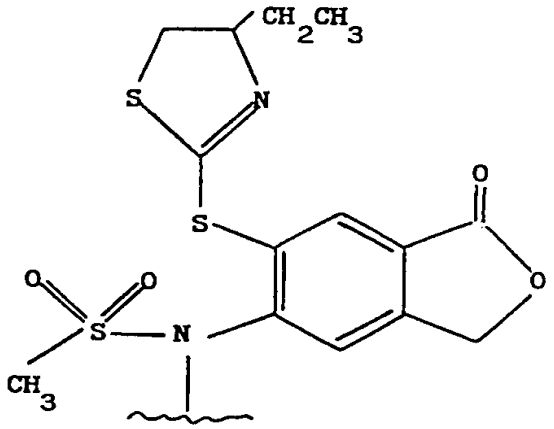
(V Ac2)



(V Ac3)

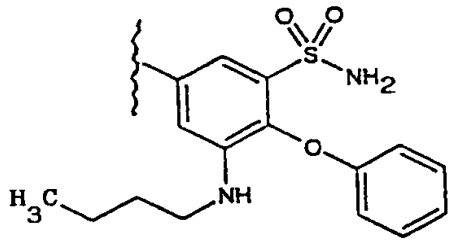


(V Ac4)

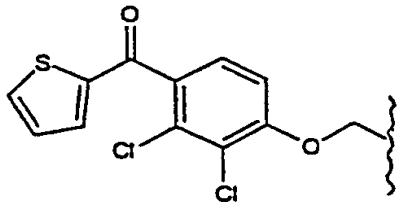


(V Ac5)

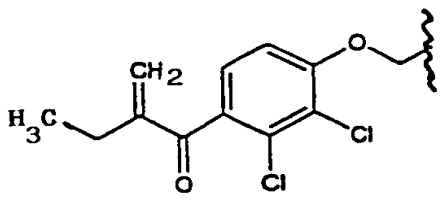
- V Ad) derivatives of diuretics when t = 1 and R is as follows:



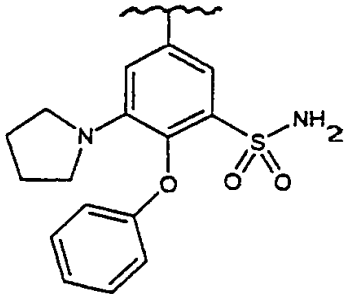
(V Ad1)



(V Ad2)

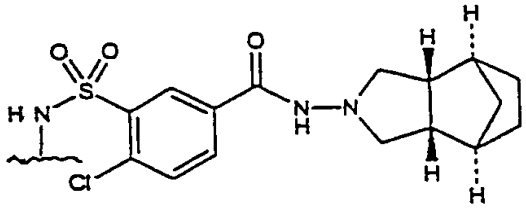


(V Ad3)

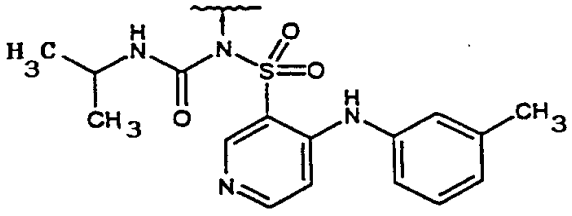


(V Ad4)

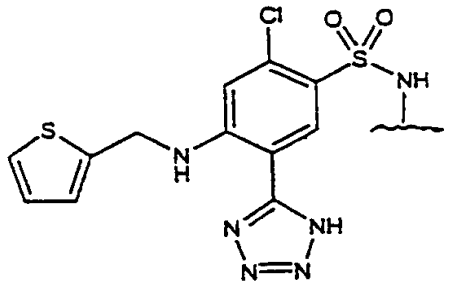
- V Ae) derivatives of diuretics when t = 0 and R is as follows:



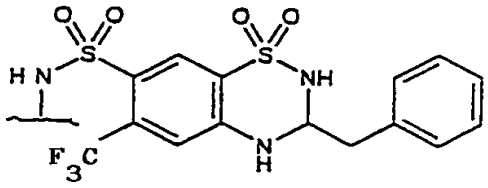
(V Ae1)



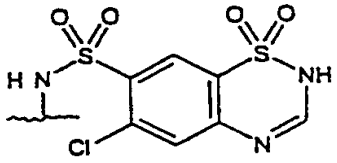
(V Ae2)



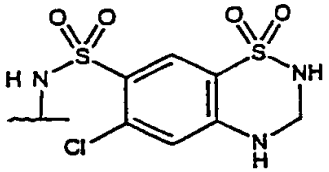
(V Ae3)



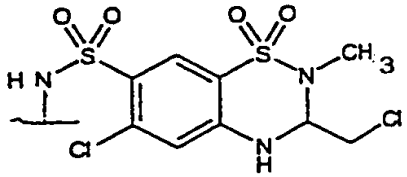
(V Ae4)



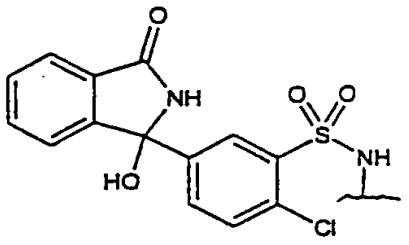
(V Ae5)



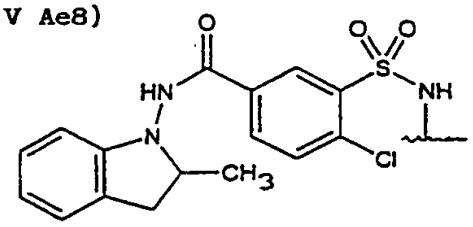
(V Ae6)



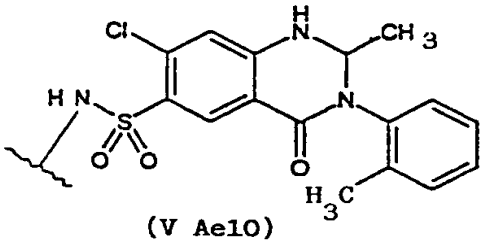
(V Ae7)



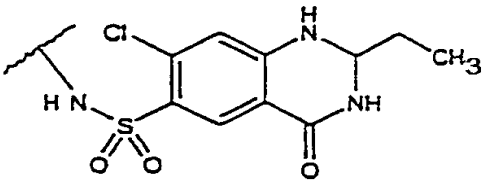
(V Ae8)



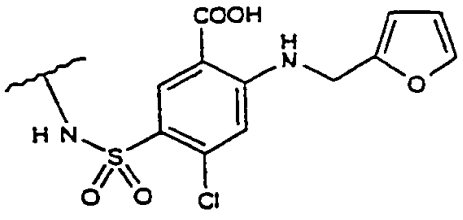
(V Ae9)



(V Ae10)



(V Ae11)



(V Ae12)

where the meaning in group V A) is as follows:

- in compounds (V Aa1) the residue of enfenamic acid, 2-[(2-phenylethyl)amino]benzoic acid, has been shown;
- in compounds (V Aa2) the residue of flufenamic acid, 2-[[3-(trifluoromethyl)phenyl]-amino]benzoic acid, has been shown;
- in compounds (V Aa3) the residue of meclofenamic acid, 2-[(2,6-dichloro-3-methylphenyl)amino]benzoic acid, has been shown;
- in compounds (V Aa4) the residue of mefanamic acid, 2-[(2,3-dimethylphenyl)amino]benzoic acid, has been shown;
- in compounds (V Aa5) the residue of tolfenamic acid, 2-[(3-chloro-2-methylphenyl)amino]benzoic acid, has been shown;
- in compounds (V Ab1) the residue of niflumic acid, 2-[[3-(trifluoromethyl)phenyl]amino]-3-pyridine carboxylic acid, has been shown;
- in compounds (V Ac1)$_{Rvac1}$ attached to the oxygen atom in position 2 of the benzene ring of N-(4-nitrophenyl)methansulphonamide can be phenyl or cycloexane. When R_{vac1} is phenyl the residue is that of nimesulide;
- in compounds (V Ac2) the residue of 3-formylamino-7-

methylsulfonylamino-6-phenoxy-4H-1-bezopyran-4-one has been shown;

- in compounds (V Ac3) the atom X_4 that links the radical 2,4-difluorothiophenyl to position 6 of the indanone ring of the residue 5-methanesulfonamido-1-indanone can be sulfur or oxygen;

- in compounds (V Ac4) the residue of celecoxib 4-[5-(4-methylphenyl)-3-(trifluoromethyl)pyrazol-1-yl] benzensulphonamide, has been shown;

- in compounds (V Ac5) the residue of 6-[2-(3-ethyl-2,3-dihydro-thiazolyl)thio-5-methanesulphonamido-3H-isobenzonfuran-1-one has been shown.

- in compounds (V Ad1) the residue of bumetanide 3-(Aminosulfonyl)-5-(butylamino)-4-phenoxybenzoic acid has been shown;

- in compounds (V Ad2) the residue of ticrynafen [2,3-Dichloro-4-(2-thienylcarbonyl)-phenoxy]acetic acid has been shown;

- in compounds (V Ad3) the residue of ethacrynic acid [2,3-Dichloro-4-(2-methylene-1-oxobutyl)phenoxy]acetic acid, has been shown;

- in compounds (V Ad4) the residue of piretanide 3-(Aminosulfonyl)-4-phenoxy-5-(1-pyrrolidinyl)benzoic

acid has been shown.

- in compounds (V Ae1) the residue of tripamide (3aα, 4α, 7α, 7aα)-3-(Aminosulphonyl)-4-chloro-N-(octaidro-4,7-metano-2H-isoindol-2-yl)benzamide has been shown.

- in compounds (V Ae2) the residue of torsemide N-[[(1-Methylethyl)amino]carbonyl]4-[(3-methylphenyl)amino]-3-pyrinesulfonamide has been shown;

-in compounds (V Ae3) the residue of azosemide 2-Chloro-5-(1H-tetrazol-5-yl)-4-[(2-thienylmethyl)amino]benzensulphonamide has been shown;

- in compounds (V Ae4) the residue of bendroflumethiazide 3,4-Dihydro-3-(phenyl-methyl)-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide has been shown;

- in compounds (V Ae5) the residue of chlorothiazide 6-Chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide has been shown;

- in compounds (V Ae6) the residue of hydrochlorotiazide 6-Chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide has been shown;

- in compounds (V Ae7) the residue of methylclothiazide (6-Chloro-3-(chloromethyl)-3,4-dihydro-2-methyl-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide has

been shown;

- in compounds (V Ae8) the residue of chlorthalidone 2-Chloro-5-(2,3-dihydro-1-hydroxy-3-oxo-1H-isoindol-1-yl)benzensulfonamide has been shown;

- in compounds (V Ae9) the residue of Indapamide 3-(Aminosulfonyl)-4-chloro-N-(2,3-dihydro-2-methyl-1H-indol-1-yl)benzamide has been shown;

- in compounds (VAe10) the residue of metolazone 7-Chloro-1,2,3,4-tetrahydro-2-methyl-3-(2-methylphenyl)-4-oxo-6-quinazolinesulfonamide has been shown;

- in compounds (V Ae11) the residue of quinetazone 7-Chloro-2-ethyl-1,2,3,4-tetrahydro-4-oxo-6-quinazoline-sulfonamide has been shown;

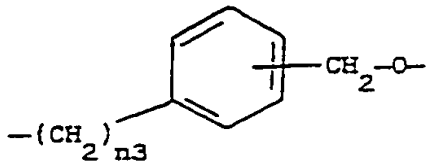
- in compounds (V Ae12) the residue of furosemide 5-(Aminosulfonyl)-4-chloro-2-[(2-furanylmethyl)amino]benzoic acid has been shown.

X_1 in formula A-X_1-NO_2 is a bivalent connecting bridge chosen from the following:

- YO

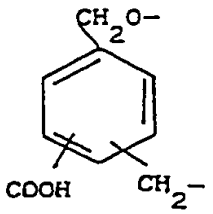
where Y is a linear or whenever possible branched C_1-C_{20} alkylene, preferably having from 2 to 5 carbon atoms, or an optionally substituted cycloalkylene having from 5 to 7 carbon atoms;

-



where n_3 is an integer from 0 to 3;

-



- $-(CH_2-CH(ONO_2)-CH_2-O)_{\overline{nf}}$,

where nf' is an integer from 1 to 6, preferably from 2 to 4;

- $(CH(R_{1f})-CH_2-O)_{\overline{nf}}$

where R_{1f} = H, CH_3 and nf is an integer from 1 to 6, preferably from 2 to 4.

2. Use of the compounds according to Claim 1, in which R is chosen from groups IV A) and V A).

3. Compounds or their compositions for use as medicaments from group V A) in Claim 1.

4. Compounds from group V A) according to Claim 1.

5. Compounds or their compositions for use as medicaments

from group V A) according to Claim 3 for the treatment of musculoskeletal disease of an inflammatory nature, respiratory disease of an inflammatory nature, gynaecological and obstetrical disease including early delivery, pre-eclampsia and dysmenorrhoea, cardiovascular disease including re-stenosis, gastrointestinal tumours.

6. Use of the following compounds, or their compositions, for the preparation of medicaments for the following therapeutical applications:

treatment of respiratory disease: bronchitis, in particular asthma: groups from I A) to V A) in Claim 1;

gynaecological and obstetrical disease including early delivery, pre-eclampsia and dysmenorrhoea: groups from I A) to V A) in Claim 1 and group VI A) as defined below;

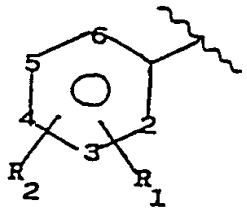
vascular disease including re-stenosis: groups from I A) to V A) in Claim 1 and group VI A);

gastrointestinal tumours: groups from I A) to V A) in Claim 1 and group VI A);

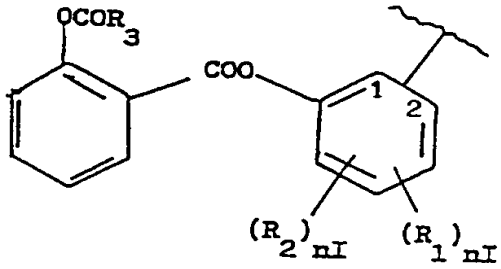
the compounds in group VI A) have the general formula

$$A\text{-}X_1\text{-}NO_2,$$

of Claim 1, where t = 1, include the following:



(Ia)



(Ib)

where:

R_1 is group $OCOR_3$; where R_3 is methyl, ethyl or a linear or branched C_3-C_5 alkyl, or the residue of a single-ring heterocycle having 5 or 6 atoms which can be aromatic, partially or totally hydrogenated, containing one or more heteroatoms independently chosen from O, N and S;

R_2 is hydrogen, hydroxy, halogen, a linear or whenever possible branched alkyl having from 1 to 4 C atoms, a linear or whenever possible branched alcoxyl having from 1 to 4 C atoms; a linear or whenever possible branched perfluoroalkyl having from 1 to 4 C atoms, for example trifluoromethyl, nitro, amino, mono- or

di(C_{1-4})alkylamino;

R_1 and R_2 jointly are the dioxymethylene group, with the proviso that when X = NH, then X_1 is ethylene and R_2 = H; R_1 cannot be $OCOR_3$ at position 2 when R_3 is methyl; nI being an integer from 0 to 1;

preferably in Ia), X is equal to O or NH, R_1 is acetoxy, preferably at position 3 or 4, most preferably in the ortho position to CO. X_1 is ethylene or $(CH_2CH_2O)_2$, R_2 is hydrogen or halogen, most preferred are the following A X_1 NO_2 compounds: 3-acetoxy-N-(2-nitroxyethyl)-benzamide, 4-acetoxy-N-(2-nitroxyethyl)-benzamide, 3-acetoxy-N-(5-nitroxypenthyl)-benzamide, 2-acetoxy-N-(5-nitroxypenthyl)-benzamide, N-2-(nitroxyethyl)-2-propionoxybenzamide, 2-acetoxy-2-nitroxyethylbenzoate, 2-acetoxy-N-(cis-2-nitroxycyclohexyl)-benzamide, 2-acetoxy-4-chloro-N-(2-nitroxyethyl)-benzamide, N-(2-nitroxyethyl)-2-((4-thiazolindinyl)carbonyloxy)-benzamide hydrochloride, 2-nicotinoyloxy-N-(2-nitroxyethyl)-benzamide, 2-acetoxy-5-nitroxypenthylbenzoate;

preferably in Ib) $R_3 = CH_3$, nI = 0;

X is equal to O, X_1 is ethylene; in this case Ib) is the residue of acetylsalicylsalicylic acid.